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Citation

Yoshida, Makiko, Paul F. Jacques, James B. Meigs, Edward Saltzman, M. Kyla Shea, Caren Gundberg, Bess Dawson-Hughes, Gerard Dallal, and Sarah L. Booth. 2008. Effect of vitamin K supplementation on insulin resistance in older men and women. *Diabetes Care* 31(11): 2092-2096.

Published Version

doi:10.2337/dc08-1204

Permanent link

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Effect of Vitamin K Supplementation on Insulin Resistance in Older Men and Women

MAKIKO YOSHIDA, PHD¹
PAUL F. JACQUES, SCD¹
JAMES B. MEIGS, MD, MPH²
EDWARD SALTZMAN, MD¹
M. KYLA SHEA, PHD¹

CAREN GUNDBERG, PHD³
BESS DAWSON-HUGHES, MD¹
GERARD DALLAL, PHD¹
SARAH L. BOOTH, PHD¹

OBJECTIVE — Vitamin K has a potentially beneficial role in insulin resistance, but evidence is limited in humans. We tested the hypothesis that vitamin K supplementation for 36 months will improve insulin resistance in older men and women.

RESEARCH DESIGN AND METHODS — This was an ancillary study of a 36-month, randomized, double-blind, controlled trial designed to assess the impact of supplementation with 500 µg/day phylloquinone on bone loss. Study participants were older nondiabetic men and women ($n = 355$; aged 60–80 years; 60% women). The primary outcome of this study was insulin resistance as measured by homeostasis model assessment (HOMA-IR) at 36 months. Fasting plasma insulin and glucose were examined as the secondary outcomes.

RESULTS — The effect of 36-month vitamin K supplementation on HOMA-IR differed by sex (sex \times treatment interaction $P = 0.02$). HOMA-IR was statistically significantly lower at the 36-month visit among men in the supplement group versus the men in the control group ($P = 0.01$) after adjustment for baseline HOMA-IR, BMI, and body weight change. There were no statistically significant differences in outcome measures between intervention groups in women.

CONCLUSIONS — Vitamin K supplementation for 36 months at doses attainable in the diet may reduce progression of insulin resistance in older men.

Diabetes Care 31:2092–2096, 2008

Limited evidence from human and animal studies suggests that vitamin K may be inversely associated with insulin resistance (1–4). In an observational study, higher dietary and supplemental vitamin K intakes were associated with greater insulin sensitivity and better glycemic status in a community-based cohort of men and women (3). In a small metabolic study of young men ($n = 12$), short-term (1-week) vitamin K supplementation improved the insulin response after an oral glucose challenge

(2). Although these studies support a potential novel role for vitamin K in insulin resistance, the available human data are limited. Furthermore, biological mechanisms behind the association between vitamin K and insulin and glucose metabolism are uncertain. Vitamin K and vitamin K-dependent proteins (prothrombin and protein S) have been identified in organs important for glucose and insulin metabolism, such as liver and pancreas (5,6). However, the function of vitamin K is not well understood beyond its

role as an enzyme cofactor for γ -carboxylation of certain glutamic acid residues in vitamin K-dependent proteins (7).

The objective of this study was to assess the effect of vitamin K supplementation for 36 months on insulin resistance, defined as the homeostasis model assessment of insulin resistance (HOMA-IR), among older men and women in a randomized, double-blind, controlled trial. The primary end point for the original trial was the 36-month change in bone mineral density of the femoral neck. We hypothesized that vitamin K supplementation at intakes attainable in the diet would have beneficial effects on insulin resistance. As secondary objectives, we also examined the effect of vitamin K supplementation on fasting plasma insulin and glucose concentrations.

RESEARCH DESIGN AND METHODS

METHODS — Men and postmenopausal women, aged 60–80 years, were recruited as part of a 36-month randomized, double-blind, controlled vitamin K supplementation trial designed to test the primary hypothesis that vitamin K supplementation would reduce age-related bone loss and vascular calcification, as described elsewhere (8). Exclusion criteria included coronary heart disease, renal disease or nephrolithiasis, liver disease, osteoporosis, and use of medications known to influence bone health. Diabetes was not an exclusion criterion, and use of insulin or oral hypoglycemic medications was allowed. However, for the purpose of the present study, we excluded subjects with diabetes from the analysis. Diabetes was defined as fasting glucose ≥ 126 mg/dl and/or self-reported use of hypoglycemic drugs or insulin medication during the study.

The subjects were advised to maintain their usual diets and to avoid taking dietary supplements other than those provided throughout the study. The treatment group received 500 µg/day phylloquinone (vitamin K₁), which is approximately five times the adequate intake for vitamin K (9), as part of an effervescent multivitamin formulation. The control group received the multivita-

From the ¹Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center, Tufts University, Boston, Massachusetts; the ²General Medicine Division and Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the ³Yale University School of Medicine, Department of Orthopaedics, New Haven, Connecticut.

Corresponding author: Sarah L. Booth, sarah.booth@tufts.edu.

Received 1 July 2008 and accepted 6 August 2008.

Published ahead of print at <http://care.diabetesjournals.org> on 12 August 2008. DOI: 10.2337/dc08-1204.

Clinical trial reg. no. NCT00183001, clinicaltrials.gov.

Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the U.S. Department of Agriculture.

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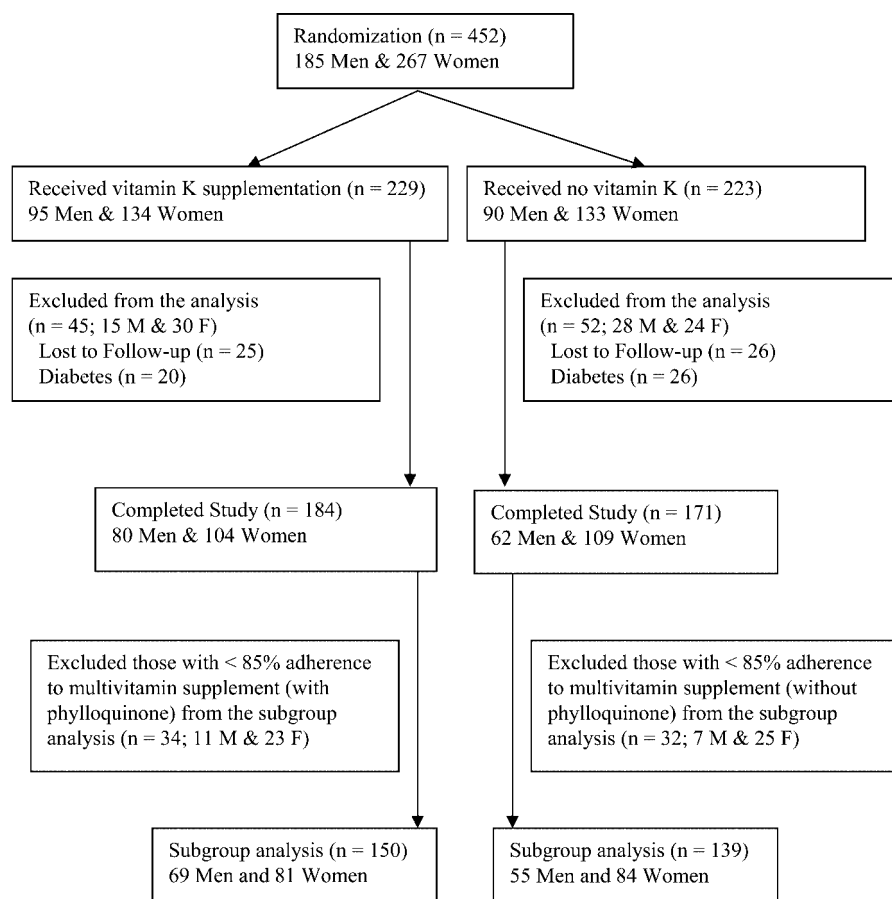


Figure 1—Study sample selection.

min formulation without phylloquinone. All study participants also received a second daily effervescent tablet containing 600 mg elemental calcium in the form of calcium carbonate and 10 μ g (400 IU) of vitamin D in the form of cholecalciferol. Detailed information on the supplements is provided elsewhere (8).

Of the original 452 participants enrolled, 355 who did not have diabetes completed the study (Fig. 1). All participants provided written informed consent, and this study was approved by the institutional review board at Tufts Medical Center.

Biochemical measurements

All blood samples were drawn between 7:00 and 10:00 A.M. after a minimum 10-h fast. Dedicated aliquots of plasma and serum were stored at -80°C and protected from light until the time of analysis. Plasma insulin was determined using Human Insulin Specific RIA kits (Linco Research, St. Charles, MO). All assays were done in duplicate, and the measurements were repeated if the total coefficient of variation (CV) of the duplicates was $>15\%$. The within-run CV of the sam-

ples was 6.4%. Plasma glucose was analyzed using the enzymatic kinetic (hexokinase-UV/NAD) method on an Olympus AU400 instrument with Olympus agents. The intra-assay CV percent was 2.0% and the interassay CV percent was 3.4%. HOMA-IR was calculated as (fasting plasma glucose [millimoles per liter] \times fasting plasma insulin [microunits per milliliter])/22.5 (10). Plasma phylloquinone and the proportion of osteocalcin that is not carboxylated (percent undercarboxylated osteocalcin) are biochemical markers for vitamin K status (11,12), and changes in these markers were examined to assess the overall efficacy of the vitamin K supplementation. Plasma concentrations of phylloquinone were measured by reverse-phase high-performance liquid chromatography (13). The total CVs for the two control samples with average phylloquinone results of 1.2 and 4.5 nmol/l were 7.4 and 8.0%, respectively. Serum total and undercarboxylated osteocalcin were measured by radioimmunoassay, using the method of Gundberg et al. (11). The total CVs for the three con-

trol samples with an average total osteocalcin result of 6.4, 14.7, and 23.8 were 8.8, 8.9, and 7.6%, respectively. Because vitamin K is a cofactor for carboxylation of specific glutamate residues, lower percent undercarboxylated osteocalcin indicates high vitamin K status (11).

Other measurements

Total body fat was measured by whole-body dual-energy X-ray absorptiometry scan using a GE Lunar model Prodigy scanner (Encore 2002 software, version 6.10.029). Leisure, household, and occupational activity was estimated with use of the Physical Activity Scale for the Elderly questionnaire (14). Tobacco and alcohol use was determined by questionnaire. Height was measured with a stadiometer and weight with a digital scale. BMI was calculated as weight in kilograms divided by the square of height in meters. Usual dietary intakes over the year before entry in the study were assessed using the Harvard food frequency questionnaire (15). Information on adherence to the supplementation (percent) was created on the basis of self-reported pill count.

Statistical analysis

SAS statistical software (version 9; SAS institute, Cary, NC) was used for all statistical analyses. Statistical significance was defined as $P < 0.05$.

The characteristics of the two study treatment groups were compared at baseline using Student's *t* test and Fisher's exact test for continuous and categorical variables, respectively. The distributions of HOMA-IR, fasting insulin, plasma phylloquinone, and phylloquinone intake were skewed to the right; thus, we analyzed these variables using the natural logarithm transformation. To assess overall efficacy of vitamin K supplementation, we examined changes in biochemical measures of vitamin K status (i.e., plasma phylloquinone and percent undercarboxylated osteocalcin) between baseline and the 36-month visit. Student's *t* test was used to compare changes of vitamin K status and other characteristics between the two study groups.

The effects of vitamin K supplementation on HOMA-IR and fasting plasma insulin and glucose concentrations were assessed by using analysis of covariance at the 6- and 36-month visits. Covariates used in the analysis were baseline outcome measures and BMI and weight change. We subsequently repeated the analysis using the 36-month change in physical activity and total body fat as additional covariates. There

Table 1—Baseline characteristics in subjects included in the primary analysis

	Men			Women		
	Control	Vitamin K	P value	Control	Vitamin K	P value
n	62	80		109	104	
Age (years)	69.7 ± 6.2	68.9 ± 5.5	0.45	67.5 ± 5.2	67.3 ± 5.5	0.77
BMI (kg/m ²)	27.0 ± 3.5	28.2 ± 4.7	0.12	26.8 ± 4.9	28.1 ± 5.8	0.07
Overweight/obese (%)*	74	71	0.70	59	72	0.04
Total body fat (%)	36.0 ± 9.8	37.8 ± 8.8	0.29	38.3 ± 9.2	36.7 ± 9.8	0.23
Physical activity scale†	136 ± 59	130 ± 65	0.61	123 ± 56	128 ± 55	0.56
Current smoking (%)	8	3	0.24	3	8	0.13
Current alcohol drinking (%)	73	70	0.85	76	70	0.36
College or greater education (%)	58	68	0.29	47	45	0.89
Blood pressure medication use (%)	34	21	0.13	29	24	0.44
Statin use (%)	29	20	0.24	24	24	1.00
Undercarboxylated osteocalcin (%)	39.9 ± 15.2	36.7 ± 15.5	0.23	42.3 ± 17.4	43.5 ± 16.2	0.62
Plasma phylloquinone (nmol/l)	1.1 ± 2	1.3 ± 1.6	0.21	1.2 ± 1.1	1.1 ± 1.4	0.37
Phylloquinone intake (μg/day)	168 ± 114	176 ± 118	0.68	180.8 ± 113.6	170 ± 96.7	0.81
Plasma glucose (mg/dl)	95.5 ± 8.1	93.1 ± 9	0.10	92 ± 9.7	93.9 ± 9.9	0.15
Plasma insulin (μU/ml)	10.5 ± 4.8	10.6 ± 5.7	0.95	10.1 ± 4.7	10.6 ± 5.5	0.78
HOMA-IR	2.5 ± 1.2	2.5 ± 1.5	0.73	2.3 ± 1.1	2.5 ± 1.4	0.33
Discontinued taking calcium supplementation (%)‡	8	6	0.75	12	11	0.83
Discontinued taking multivitamin supplements (%)	8	6	0.75	8	9	1.00

Data are means ± SD or % for continuous and categorical variables, respectively. For statistical analysis, logarithm transformation was performed for plasma insulin, HOMA-IR, plasma phylloquinone, and phylloquinone intakes. Phylloquinone intake included both dietary and supplemental sources of phylloquinone. *Defined as BMI >25 kg/m². †The physical activity scale was calculated on the basis of the questionnaire that captures leisure, household, and occupational activity (14). Higher scores indicate more physically active condition. ‡Discontinued taking calcium and vitamin D supplementation.

was one potential outlier who had an extremely high plasma fasting insulin concentration (fasting insulin of 82.3 μU/ml). This participant was removed from the HOMA-IR and fasting insulin analysis, although inclusion or exclusion of this potential outlier did not significantly change the results. We also repeated analyses with two sets of data excluding participants with <85% adherence to vitamin K supplement ($n = 66$) or including those with diabetes ($n = 46$) to assess the stability of the findings.

We tested for statistical interaction between vitamin K intervention and sex. Because we observed significant interactions between sex and treatment group in HOMA-IR and plasma fasting insulin at the 36-month visit (HOMA-IR $P = 0.02$; insulin $P = 0.01$), men and women were analyzed separately. With our overall sample size of 355 and significant between-group difference in HOMA-IR of 0.44, with a between-group SD of 1.4, there was an 82% chance that the hypothesis of no supplement effect would be rejected at the 0.05 level of significance. However, upon stratification by sex, the statistical power was reduced to 44% in men and 62% in women.

To explore a possible explanation for the observed sex interaction, we exam-

ined the associations between plasma phylloquinone concentrations and BMI. We calculated plasma triglyceride-adjusted Pearson's partial correlation coefficients (Pearson's partial r).

RESULTS— The baseline characteristics are summarized in Table 1. Participant characteristics were comparable between the two treatment groups in both men and women, with the exception of higher prevalence of overweight or obesity among women in the vitamin K-treated group.

In the vitamin K-treated group, 36-month changes in plasma phylloquinone and percent undercarboxylated osteocalcin were significantly different from those of the control group for both men and women ($P < 0.001$). The mean ± SD 36-month changes in plasma phylloquinone concentrations for men and women receiving the vitamin K supplement were 1.4 ± 2.5 and 2.3 ± 2.8 nmol/l, respectively, whereas the changes in the men and women in the control group were -0.2 ± 1.9 and 0.1 ± 1.3 nmol/l, respectively. The 36-month changes in percent undercarboxylated osteocalcin were $-19.0 \pm 23.4\%$ for men and $-19.3 \pm 20.5\%$ for women in the treated group

and $0.4 \pm 17.7\%$ for men and $2.3\% \pm 21.2\%$ for women in the control group.

HOMA-IR and plasma insulin concentrations were statistically significantly lower at the 36-month visit among men in the supplement group versus men in the control group after adjustment for baseline HOMA-IR, BMI, and weight change (Table 2). There was no significant difference among men in HOMA-IR and plasma insulin at the 6-month visit. When statistical analyses were repeated using the 36-month change in physical activity and percent body fat as additional covariates, differences among men in HOMA-IR were still statistically different ($P = 0.03$), whereas there was attenuation in differences in the plasma insulin ($P = 0.07$). When statistical analyses were restricted to those with $\geq 85\%$ adherence, similar results were noted for 36-month changes in HOMA-IR and plasma insulin among men (vitamin K-treated group versus control group: HOMA-IR, -0.11 [95% CI -0.40 to 0.19] vs. 0.47 [0.15 to 0.80], $P = 0.01$; insulin, -0.46 [-1.56 to 0.65] vs. 1.47 [0.22 to 2.71], $P = 0.03$). Fasting plasma glucose concentrations among men did not differ between two study groups at any time point. There were no statistically significant differences in changes in HOMA-IR, fasting plasma

Table 2—Changes for HOMA-IR, fasting plasma insulin, and glucose concentrations for vitamin K and non-vitamin K supplementation

Outcomes and change	Model	Men			Women		
		Control	Vitamin K	P value	Control	Vitamin K	P value
n		62	80		109	104	
HOMA-IR							
6 months	Crude	0.02 (−0.22 to 0.25)	0.06 (−0.15 to 0.27)	0.77	−0.03 (−0.19 to 0.14)	0.04 (−0.13 to 0.20)	0.61
6 months	Adjusted	0.03 (−0.21 to 0.27)	0.05 (−0.16 to 0.26)	0.91	−0.01 (−0.17 to 0.15)	0.02 (−0.14 to 0.19)	0.76
36 months	Crude	0.35 (0.03 to 0.68)	−0.09 (−0.37 to 0.20)	0.05	0.16 (−0.04 to 0.37)	0.31 (0.10 to 0.52)	0.32
36 months	Adjusted	0.39 (0.09 to 0.69)	−0.12 (−0.38 to 0.15)	0.01	0.19 (0.00 to 0.38)	0.28 (0.09 to 0.48)	0.49
Plasma insulin (μU/ml)							
6 months	Crude	−0.34 (−1.27 to 0.59)	−0.2 (−1.02 to 0.63)	0.82	−0.68 (−1.34 to −0.03)	−0.19 (−0.86 to 0.48)	0.30
6 months	Adjusted	−0.29 (−1.22 to 0.65)	−0.23 (−1.06 to 0.59)	0.93	−0.60 (−1.24 to 0.04)	−0.28 (−0.93 to 0.38)	0.49
36 months	Crude	1.08 (−0.15 to 2.30)	−0.43 (−1.51 to 0.64)	0.07	0.23 (−0.50 to 0.97)	1.08 (0.33 to 1.83)	0.12
36 months	Adjusted	1.16 (0.02 to 2.30)	−0.49 (−1.50 to 0.51)	0.04	0.37 (−0.32 to 1.06)	0.94 (0.23 to 1.64)	0.26
Plasma glucose (mg/dl)							
6 months	Crude	3.41 (1.79 to 5.04)	3.52 (2.09 to 4.96)	0.92	2.28 (0.80 to 3.75)	2.31 (0.80 to 3.82)	0.97
6 months	Adjusted	3.70 (2.08 to 5.32)	3.30 (1.87 to 4.72)	0.72	2.43 (0.98 to 3.88)	2.16 (0.67 to 3.64)	0.80
36 months	Crude	2.15 (0.20 to 4.10)	0.98 (−0.75 to 2.72)	0.38	1.51 (−0.04 to 3.05)	1.33 (−0.24 to 2.91)	0.88
36 months	Adjusted	2.57 (0.70 to 4.44)	0.65 (−1.01 to 2.31)	0.14	1.68 (0.17 to 3.18)	1.16 (−0.38 to 2.69)	0.64

Data are least-squares means (95% CI). Least-squares means are the mean changes in the outcomes when individual values covariates are held constant. Crude analysis was adjusted for the baseline outcome measure (HOMA-IR, plasma insulin, or glucose). Adjusted analysis controlled for baseline outcome measures, baseline BMI, and either 6- or 36-month weight change.

insulin, and glucose between women in the vitamin K-treated groups and control group. Repeating the analyses including diabetic individuals did not affect our findings (data not shown).

In analysis performed to examine a possible reason for the discrepancy between findings for men and women, we found that plasma phylloquinone concentrations were inversely associated with BMI in women, but not in men, after adjustment for plasma triglycerides (Pearson's partial $r = -0.15$, $P = 0.02$). In contrast, percent body fat was not correlated with plasma phylloquinone concentrations in men or women. Among women in our study, there was a significant increase in mean percent body fat of 0.6% over the 36 months ($P = 0.002$), whereas body weight did not change significantly. In men, mean body weight decreased by 0.5 kg ($P = 0.02$) and body fat increased by 0.5% ($P = 0.001$), respectively. There were no statistically significant changes in physical activity for men or women.

CONCLUSIONS— The major finding of this study was that daily supplementation with 500 μg of phylloquinone for 36 months had a protective effect on progression of insulin resistance in older men.

In an animal study, rats fed a low vitamin K diet had impaired early insulin

response and subsequent increased insulin secretion after intravenous administration of glucose (1). Higher vitamin K intake was cross-sectionally associated with reduced insulin resistance in both men and women in the Framingham Offspring cohort (3). A metabolic study of young men showed a significant association between vitamin K and post-glucose challenge measures, but not fasting measures (2). In our study, a beneficial effect of vitamin K supplementation for 36 months was observed using fasting measures of insulin resistance. The effect of this intervention on post-glucose challenge measures of insulin resistance was not tested in our study.

Recent studies proposed that the uncarboxylated form of osteocalcin, a vitamin K-dependent bone protein, may improve insulin sensitivity and increase β-cell insulin secretion partially through the enhancement of β-cell proliferation, energy expenditure, and adiponectin expression in mice (16,17). In our study, men receiving vitamin K supplementation had less uncarboxylated osteocalcin than the control group, which does not support the findings of the animal studies. Alternatively, it is plausible that vitamin K may improve insulin sensitivity through suppression of inflammation. In vivo and in vitro studies have shown that vitamin K

reduced lipopolysaccharide-induced inflammation (18,19). More recently, it was reported that biochemical and dietary measures of vitamin K status were inversely associated with inflammatory markers in an observational study (20).

The beneficial effect of vitamin K on insulin resistance was limited to men in this study. However in a recent observational study, the inverse association between vitamin K intake and insulin resistance was observed in men and women (3). In a previous metabolic study, only young men were studied (2), and there are no other studies with which to make a comparison. Although adjustment of BMI in the statistical model did not change our finding in women, one potential explanation for this lack of protective effect of vitamin K on insulin resistance in women is the role of adipose tissue in modulating the response to vitamin K supplementation. In our study, overweight or obesity, which are major determinants of insulin resistance (21, 22), was more prevalent in women who received vitamin K supplementation than in those who did not. Furthermore, there was an inverse association between plasma phylloquinone concentrations and BMI in the women, which is suggestive of an impaired response to vitamin K supplementation. It may be plausible that adipose tissue

stores the fat-soluble vitamin K, which may render the vitamin K unavailable for peripheral organs. In the absence of data on the role of adipose tissue in vitamin K metabolism, this suggestion is currently speculative. Alternatively, it is plausible that our study was statistically underpowered to detect statistically significant differences in HOMA-IR in response to vitamin K supplementation among women.

The interpretation of these findings is limited by several factors. First, this study was based on the analyses of data obtained from a study designed to determine the effect of vitamin K supplementation on changes in bone mineral density and vascular calcification in older men and women. Our findings may not be representative of the general population owing to the exclusion criteria of the parent study, and measures presented in this study were not necessarily obtained by optimal techniques. We acknowledge that use of the hyperinsulinemic-euglycemic clamp would have provided a more direct measure of insulin secretion and sensitivity than HOMA-IR, which only provides an indirect estimate of insulin resistance. Likewise, our assessment of body composition was limited to BMI and percent body fat as measured by dual-energy X-ray absorptiometry and did not provide information on regional adiposity. We also had limited statistical power to detect differences in HOMA-IR in response to vitamin K supplementation, which may explain the null findings in women. Finally, most of our participants were Caucasians; thus, our findings need to be examined in other populations.

In summary, 36 months of vitamin K supplementation had a beneficial effect on insulin resistance in older men but not in older women. As the parent study was not designed to test this hypothesis, these findings need to be replicated in a study designed specifically to test the hypothesis that vitamin K plays a protective role in insulin resistance in older adults.

Acknowledgments—This work was supported by the U.S. Department of Agriculture, Agricultural Research Service, under Cooperative Agreement 58-1950-7-707, the National Institutes of Health (AG14759, HL69272, TH32 HL69772-01A1, and AR38460), and the American Heart Association (0515605T). M.Y. was supported by a Graduate Student Scholarship from the Ministry of Education, Culture, Sports and Technology of Japan. J.B.M. was supported by a Career Development Award from the American Diabetes As-

sociation and by National Institute of Diabetes and Digestive and Kidney Diseases Grant K24 DK080140. Hermes Arzneimittel, Munich, Germany, generously donated the supplements used for this study.

The authors express their appreciation to James Peterson, Nancy Palermo, Anne Charette, Molly Damon, the staff of the Metabolic Research Unit and Nutrition Evaluation Laboratory, and all the study participants for their invaluable contribution to this study.

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